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### **REMARKS**

Claims 1-7 and 12 were pending. Claims 13, 16, and 19 are cancelled without prejudice to pursuing these claims in this or other continuing applications. Claims 1, 14, 17, 18, and 20 have been amended. Claims 23-28 are new. Claims 23-26 represent previously cancelled Claims 8-11. Upon entry of the present amendments, Claims 1-7, 12, 14-15, 17-18 and 20-28 will be pending in this application. A copy of the claims showing amendments made therein is attached hereto as Exhibit A. A copy of the pending claims is attached hereto as Exhibit B.

Claims 1 and 18 have been amended to recite that  $\alpha$ ,  $\beta$  unsaturated aryl sulfone is administered at least about 4 hours before the administration of a mitotic phase cell cycle inhibitor or a topoisomerase inhibitor. Claims 1 and 18 have additionally been amended to recite specific classes of the compounds of mitotic phase cell cycle inhibitors and topoisomerase inhibitors. Support for these amendments can be found, *inter alia*, in Claims 13, 16, page 17, lines 16-18, and page 14 of the specification.

Claims 14, 17 and 20 have been amended to correct the antecedent basis of these claim.

Claims 23-26 are new and represent cancelled Claims 8-11, respectively. Support for these Claims can be found, *inter alia*, in cancelled Claims 8-11.

Claims 27-28 are new. These claims are dependent upon base Claims 1 and 18, respectively and limit the species of animals to human beings. Support for this amendment can be found, *inter alia*, on page 4, lines 1-2, and page 58, Example 7.

The amendments to the claims do not constitute new matter as defined under 35 U.S.C. § 132. Applicants respectfully request entry of the amendments.

#### **I. INTERVIEW WITH THE EXAMINER**

Applicants would like to extend their gratitude to the interview graciously granted by Examiner Podmanabhan and Examiner Bahar to Applicants. In the interview the Examiners suggested that an amendment to Claim 1 to incorporate limitations of Claim 13 (time of

administration) and Claim 16 (specific inhibitors) into Claim 1 would place the claims in a better condition for allowance.

Without acquiescing in the propriety of the Examiner's proposed amendments, and solely to advance prosecution of this application, Applicants have amended Claims 1 and 18 to recite the time of administration and specific type of inhibitors, as requested by the Examiners. Any subject matter excluded from claims 1 and 18 by these amendments is expressly not disclaimed and is deemed by Applicants to be patentable over the art of record. Applicants preserve rights to pursue original Claims 1 and 18 in this or other continuing applications.

## II. ELECTION OF SPECIES

In the Office Action dated April 10, 2001 (Paper No. 4) the Examiner issued an election of species requirement among the claims as governed by MPEP 809.02. The Examiner stated that Applicants are required to elect a specific arylsulfone compound for examination purposes and that Applicants' response must include an identification of the species and listing of claims readable thereon. Applicants responded to the election of species requirement by electing the species of the claims which utilize the compound 4-carboxystyryl-4-chlorobenzylsulfones. In the Office Action dated April 10, 2002 (Paper No. 12) the Examiner inadvertently mischaracterized the requirement as being a restriction requirement and stated that a complete response to the rejection must include cancellation of non-elected claims. The Examiner cited 37 C.F.R. § 1.144 and MPEP 821.01 to support this position.

Applicants respectfully submit that the Examiner has apparently confused the two different examination practices, namely, restriction requirement and election of species. As is evident from the prosecution history of this case, Claims 8-11 of this application were subjected to an election of species and not a restriction requirement. For a complete response to the Office Action, contrary to the Examiner's request, Applicants were not required to cancel claims directed to the non-elected species. The authority cited by the examiner in Paper No. 12 does not support cancellation of claims directed to non-elected species and does not directly relate to the election of species requirement.

A complete response for election of species requires identification of genus and all claims readable thereupon MPEP 809.02 (b). Applicants are entitled to consideration of claims to a reasonable number of disclosed species. When a generic claim is subsequently found to be allowable and not more than a reasonable number of additional species are claimed, Applicants should be advised of the allowable generic claim and that claims drawn to the non-elected species are no longer withdrawn since they are fully embraced by the allowed generic claims. MPEP 809.02 (c).

Accordingly, Applicants submit that new Claims 23-26, which restate original Claims 8-11 that were previously cancelled in response to the Examiner's inadvertent erroneous request for canceling these claims, should now be entered. Similar to Claims 8-11, Claims 23-26, are fully embraced by Claim 1 and thus would be allowable upon allowance of Claim 1.

### **III. REJECTION OF CLAIMS UNDER 35 U. S. C. § 103 (a)**

The Examiner rejected Claims 1-7 and 12-22 under 35 U.S.C. § 103 (a) as allegedly being obvious over Reddy in view of Griggs. The Examiner asserts that Reddy teaches styryl sulfone compounds employed in a method of treating breast and prostate tumor cells, and induce apoptosis of such tumor cells while sparing normal cells. Specifically, the Examiner states that:

[R]eddy teaches that its aryl sulfones are effective anti-tumor agents, yet they "spare" normal cells. The sparing of the normal cells means that the incidence of side effects (on normal cells) is reduced if not eliminated. Therefore Reddy does indeed teach the employment of aryl sulfones as cytoprotective agents.

The Office Action, Paper No. 16, page 4, lines 5-9.

While the Examiner acknowledges that Reddy does not teach a method of administration of an  $\alpha$ ,  $\beta$  unsaturated aryl sulfone prior to the administration of mitotic phase cell cycle or topoisomerase inhibitors, it is the Examiner's position that Griggs allegedly cures this deficiency by teaching that cytoprotective agents used in combination with anticancer therapy reduce

treatment-related toxicity of anticancer therapy. The Examiner, therefore, alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ an anticancer drug along with a cytoprotective agent such as the styryl sulfone compounds of Reddy to arrive at the claimed invention. To provide the requisite motivation to combine the references, the Examiner specifically states that:

[o]ne of ordinary skill in the art would have been motivated to employ an anti-cancer drug along with a cytoprotective agent such as the styryl sulfone compound of Reddy *et al.* because both compounds are known to be effective in treating cancer and that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be useful for the very same purpose.

Office Action, Paper No. 16, page 3, lines 10-14.

Applicants respectfully traverse the Examiner's rejections for the following reasons.

At the outset, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness. As the Examiner is no doubt aware, three basic criteria must be met to establish a case of *prima facie* obviousness under 35 U.S.C. § 103.

First, there must have been at the time of the invention a motivation to combine the references cited. *In re Jones*, 958 F.2d 347 (Fed. Cir. 1992); *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988)(holding that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art). *Ecolchem, Inc., v. Southern California Edison Company*, 227 F.3d 1361, 1372 (Fed. Cir. 2000), citing *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577 (Fed. Cir. 1984)(holding obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination).

The Federal Circuit has suggested that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. *Id.* This is because "when prior art references require selective combination by the court to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself." *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1142 (Fed. Cir. 1985).

Hindsight cannot be used to reject a claim as obvious. *In re Sernaker*, 702 F.2d 989, 994 (Fed. Cir. 1983); *In re Rinehart*, 531 F.2d 1048 (CCPA 1976); *In re Imperato*, 486 F.2d 585 (CCPA 1973); *In re Adams*, 356 F.2d 998 (CCPA 1966). Consequently, it is legally improper to select from the prior art the separate components of the inventor's combination, using the blueprint supplied by the inventor. *C.R. Bard Inc. v. M3 Systems, Inc.*, 157 F.3d 1340, 1352 (Fed. Cir. 1998) citing *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 (Fed. Cir. 1985)(holding the prior art must suggest to one of ordinary skill in the art the desirability of the claimed combination).

Second, the alleged prior art must teach or suggest all of the limitations of the claims alleged to be obvious. *In re Royka*, 490 F.2d 981 (CCPA 1974)(holding that to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art).

Third, there must have been at the time of the invention a reasonable expectation of success for arriving at the claimed invention. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991)(holding that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure); *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1207-1208 (Fed. Cir.), cert. denied 502 U.S. 856 (1991) *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995).

Applicants respectfully submit that the Examiner has failed to make a *prima facie* case of obviousness against the invention as claimed. The Examiner has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Piasecki*, 745 F.2d 1468, 1471-1472 (Fed. Cir. 1984). The Examiner can satisfy this burden only by demonstrating some objective

teaching in the prior art or showing that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. *In re Lahu*, 747 F.2d 703, 705 (Fed. Cir. 1984). Additionally, the Examiner must show that the references properly combined teach each and every element of the claimed invention. Applicants respectfully submit that the Examiner has not met this burden.

**A. THE CITED REFERENCES DO NOT SUGGEST THE CLAIMED INVENTION**

Applicants respectfully submit that a rejection under 35 U.S.C. § 103 requires that the Examiner show that the references properly combined teach each and every element of the claimed invention. The Examiner has not met this burden. Claims 1-7 and 12-22 are directed to methods in which an animal (inclusive of humans) is protected from cytotoxic side effects of mitotic phase cell cycle or topoisomerase inhibitors by administering at least one cytoprotective  $\alpha$ ,  $\beta$  unsaturated aryl sulfone compound before treatment with the mitotic phase cell cycle or topoisomerase inhibitors.

Neither Reddy nor Griggs, either alone or in combination, teaches or suggests the invention as claimed. The legally required suggestion of each and every element of the pending claims, namely, a specific method of therapy for “protection of an animal”, from a specific disorder, “cytotoxic side effects” resulting from the use of a specific class of drugs, “mitotic phase cell cycle or topoisomerase inhibitors”, by the use of a specific compound, “ $\alpha$ ,  $\beta$  unsaturated aryl sulfone”, in a specific manner, “prior to the administration of the mitotic phase cell cycle or topoisomerase inhibitors”, are simply not present in Reddy or Griggs, either alone or in combination.

Specifically, there is no suggestion in Reddy for the use of an  $\alpha$ ,  $\beta$  unsaturated aryl sulfone as a cytoprotective agent. The Examiner alleges that Reddy teaches that aryl sulfone compounds are cytoprotective agents because Reddy states that these compounds are cytotoxic to tumor cells but “spare normal cells.” Applicants respectfully submit that the Examiner’s characterization of this statement is incorrect. Contrary to the Examiner’s assertion, the

statement in Reddy, regarding sparing of normal cells, does not teach the use of aryl sulfone compounds as a cytoprotective agent. Rather, the statement merely suggests that aryl sulfone compounds are specific anticancer drugs that exclusively attack cancer cells, while not harming normal cells.

Applicants respectfully submit that the specificity of an anticancer drug against a particular cancer does not render that anticancer drug a “cytoprotective agent” for normal cells. If the interpretation of the Examiner for the phrase “sparing normal cells” was correct, then a majority of the current anticancer drugs that specifically affect cancer cells while sparing normal cells would have also been regarded as cytoprotective agents. Clearly, this is not the case.

The Examiner further alleges that

“[A]ssuming *arguendo* that Reddy does not teach the cytoprotective qualities of aryl sulfones, at the very least Reddy teaches that styryl sulfone compounds are known to be effective in treating cancer. It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be useful for the very same purpose.”

The Examiner appears to suggest that it would be obvious to combine Reddy and Griggs as each separately teaching an anticancer agent. The Examiner’s position is untenable for the following reasons.

First, contrary to the Examiner’s contention, Griggs does not teach that amifestone is an anticancer drug. Second, assuming, *arguendo*, that it was obvious to combine Griggs and Reddy, on the basis of the Examiner’s incorrect interpretation that Griggs teaches an anticancer agent, there is no teaching or suggestion in the combination for a method of protecting normal cells from cytotoxicity as claimed. Third, the combined references do not teach the claimed order of administration of the first and second drug. The claims specifically require administration of an  $\alpha$ ,  $\beta$  unsaturated aryl sulfone compound prior to the administration of mitotic phase cell cycle or topoisomerase inhibitors. The specification specifically teaches that simultaneous exposure of  $\alpha$ ,



$\beta$  unsaturated aryl sulfone and the inhibitor does not result in protection. *See*, specification at page 15, last paragraph.

Griggs merely discloses that amifostine protects normal cells from the cytotoxic effects of alkylating agents, paclitaxel, and radiation. Amifostine is an organic thiophosphate homolog of cysteamine; *see* entry for “amifostine” from The Merck Index (12<sup>th</sup> Edit.), Budavari *et al.*, eds., Merck & Co., Inc., Whitehouse Station, NJ, 1996, attached herewith as Exhibit C. It was also known at the time the present application was filed that more amifostine is taken up by normal cells than by tumor cells, which accounts for the drug’s cytoprotective properties. *See, i.e.*, the abstract entitled “Cytoprotectant Amifostine Approved” accessed from

<http://www.slip.net/~mcdavis/database/amifos2.htm>

on July 18, 2002, attached herewith as Exhibit D, which references Spencer, C.M., *et al.*, (1995), *Drugs* 50: 1001-1031.

There is no mention in Griggs of  $\alpha$ ,  $\beta$  unsaturated aryl sulfone compounds, less so their use as a cytoprotective agent equivalent to amifostine. Even assuming *arguendo* that Reddy somehow teaches the use of  $\alpha$ ,  $\beta$  unsaturated aryl sulfones as cytoprotectants, the mere fact that both compounds are cytoprotectants is not sufficient, absent some other indication in the prior art, that amifostine and  $\alpha$ ,  $\beta$  unsaturated aryl sulfones are interchangeable. M.P.E.P. 2144.06. The Examiner has not identified any teaching in the prior art showing that amifostine and the  $\alpha$ ,  $\beta$  unsaturated aryl sulfones are equivalent cytoprotectants.

As can be seen from the Merck Index entry, *supra*, the chemical structures of the  $\alpha$ ,  $\beta$  unsaturated aryl sulfones and amifostine are completely unrelated. There is also no evidence in Reddy or Griggs that  $\alpha$ ,  $\beta$  unsaturated aryl sulfones have a differential uptake in normal vs. tumor cells akin to amifostine. Moreover, the mechanism of action of amifostine and  $\alpha$ ,  $\beta$  unsaturated aryl sulfones appears to be different: amifostine protects normal cells from alkylating agents (*see*, Griggs), while  $\alpha$ ,  $\beta$  unsaturated aryl sulfones do not (*see*, the specification at page 51, lines 16-19 and Table 6).

Amifostine and  $\alpha$ ,  $\beta$  unsaturated aryl sulfones disparate chemical structures, different mechanisms of action, and potentially dissimilar pharmacology demonstrate that these compounds are not equivalent. Thus, even if the Examiner’s interpretation of Reddy were taken

as correct, one of ordinary skill in the art following the teachings of Reddy and Griggs would not arrive at the presently claimed invention.

As the Board has asserted in *Ex parte Clapp*, “[t]o support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the Examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references.” *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). In this case, the cited references do not suggest the claimed invention because 1) Reddy does not disclose or suggest that  $\alpha$ ,  $\beta$  unsaturated aryl sulfone compounds are cytoprotective agents; 2) Reddy does not disclose or suggest the administration of  $\alpha$ ,  $\beta$  unsaturated aryl sulfone compounds prior to administering a separate mitotic phase cell cycle or topoisomerase inhibitor for protecting normal cells from those inhibitors; 3) the chemical structure of the  $\alpha$ ,  $\beta$  unsaturated aryl sulfones and amifostine are unrelated; and 4) the Reddy’s  $\alpha$ ,  $\beta$  unsaturated aryl sulfones and amifostine do not share similar pharmacokinetic characteristics.

Accordingly, Applicants submit that the cited references, either alone or in combination, does not teach or suggest each and every element of the claimed invention.

Notwithstanding the above, without acquiescing with the Examiner’s rejections and solely to advance prosecution of this application, Applicants have amended Claims 1 and 18 to recite the specific classes of the inhibitor and the time interval of at least four hours prior to administration of the inhibitor. These amendments were made to strictly recite an embodiment of the claimed method of the invention. Any subject matter excluded from claims 1 and 18 by these amendments is expressly not disclaimed and is deemed by the Applicant to be patentable, as these amendments are made without prejudice to the filing of a continuation application.

Applicants respectfully request withdrawal and reconsideration of the Examiner’s rejection.

**B. NO MOTIVATION TO COMBINE THE REFERENCES**

Applicants respectfully submit that the Examiner has failed to establish the legally required motivation to combine the references. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 682 (Fed. Cir. 1990)(emphasis added) citing *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984)(the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification). In the instant case, there is no such suggestion to combine the references cited by the Examiner.

One of ordinary skill in the art following the teachings of Reddy would have no need, desire, or reason to look to a reference that suggests the use of a cytoprotective agent to protect normal cells from the adverse effects of an anticancer drug simply because Reddy itself teaches that aryl sulfone compounds are anticancer drugs that do not harm normal cells. Similarly, one of ordinary skill in the art following the teachings of Griggs would have no need, desire, or reason to look to Reddy for the use of aryl sulfones, either as an anticancer drug or as a cytoprotective agent, because Griggs' anticancer regimen does not include the use of an aryl sulfone compound as an anticancer drug and its cytoprotective agent "amifestone" is structurally and functionally very different from aryl sulfones.

Neither Reddy nor Griggs suggests the desirability of using a specific anticancer drug as a cytoprotective agent prior to the administration of a second drug, as required by the claims of this application. Because there is no teaching or suggestion for using  $\alpha$ ,  $\beta$  unsaturated aryl sulfone compounds as cytoprotectants before an anticancer or anti-inflammatory drug prior to Applicants' disclosure, the Examiner's interpretation of Reddy and Griggs must derive from impermissible hindsight reconstruction using the present specification.


Here, the cited references carry no relationship except that imposed by the present specification and claims. Once removed from the context of Applicant's disclosure, the references fragment into a collection of unrelated disclosures with little bearing on the claimed invention. Any motivation to combine the teachings of the cited references is the result of

impermissible hindsight. Thus, Applicants submit that the requisite suggestion or motivation for one of ordinary skill in the art to arrive at the elements of the claimed invention is absent. Because the suggestion to combine Reddy and Griggs is absent from the cited references, Applicants respectfully request that the Examiner withdraw the rejection of the claims.

### CONCLUSION

In light of the above, Applicants respectfully submit that all claims are allowable over the art of record, and a Notice of Allowance is courteously solicited. The foregoing is submitted as a full and complete response to the Office Action dated November 5, 2002, (Paper No. 16) and the Examiner interview dated April 1, 2003 (Paper No. 17). The Examiner is invited and encouraged to contact the undersigned attorney of record if such contact will facilitate an efficient examination and allowance of the application

Respectfully submitted,  
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## EXHIBIT A

### A MARKED UP VERSION OF THE CLAIMS SHOWING THE AMENDMENTS MADE HEREIN

1. (Twice Amended) A method for protecting an animal from cytotoxic side effects of the administration of a mitotic phase cell cycle inhibitor or a topoisomerase inhibitor comprising administering to the animal, at least about 4 hours before administration of the inhibitor ~~in advance of administration of said inhibitor~~, an effective amount of at least one cytoprotective  $\alpha$ ,  $\beta$  unsaturated aryl sulfone compound, wherein the mitotic phase cell cycle inhibitor is selected from the group consisting of vinca alkaloids, taxanes, naturally occurring macrolides, and colchicine and its derivatives and the topoisomerase inhibitor is selected from the group consisting of camptothecin, etoposide and mitoxantrone. ~~and topoisomerase inhibitor are other than an  $\alpha$ ,  $\beta$  unsaturated aryl sulfone compound.~~

14. (Once Amended) The method according to claim 1 ~~13~~ wherein the cytoprotective compound is administered at least about 12 hours before administration of the mitotic phase cell cycle inhibitor or topoisomerase inhibitor.

17. (Once Amended) The method according to claim 1 ~~16~~ wherein the mitotic phase cell cycle inhibitor is selected from the group consisting of paclitaxel and vincristine.

18. (Thrice Amended) In a method for treating cancer or other proliferative disorder comprising administering an effective amount of at least one mitotic phase cell cycle inhibitor or topoisomerase inhibitor to an animal in need of such treatment, the improvement comprising administering to ~~said~~ the animal at least about 4 hours prior to administration of ~~said~~ the mitotic phase cell cycle inhibitor or topoisomerase inhibitor an effective amount at least one cytoprotective  $\alpha$ ,  $\beta$  unsaturated aryl sulfone compound, wherein the mitotic phase cell cycle inhibitor is selected from the group consisting of vinca alkaloids, taxanes, naturally occurring macrolides, and colchicine and its derivatives and the topoisomerase inhibitor is selected from the group consisting of camptothecin, etoposide and mitoxantrone ~~and topoisomerase inhibitor~~

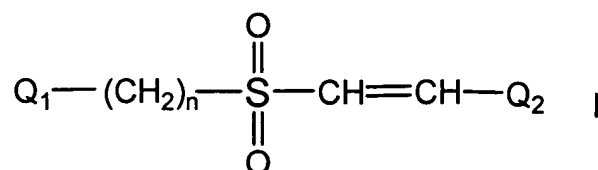
~~are other than an  $\alpha$ ,  $\beta$  unsaturated aryl sulfone compound~~, and wherein the animal is protected from the cytotoxic side effects of the administration of ~~said~~ the mitotic phase cell cycle inhibitor or topoisomerase inhibitor.

20. (Once Amended) The method according to claim 18 ~~19~~ wherein the cytoprotective compound is administered at least about 12 hours before administration of the mitotic phase cell cycle inhibitor or topoisomerase inhibitor.

**EXHIBIT B****A COPY OF THE CLAIMS THAT WILL BE PENDING UPON ENTRY OF THE PRESENT AMENDMENTS**

1. A method for protecting an animal from cytotoxic side effects of the administration of a mitotic phase cell cycle inhibitor or a topoisomerase inhibitor comprising administering to the animal, at least about 4 hours before administration of the inhibitor, an effective amount of at least one cytoprotective  $\alpha$ ,  $\beta$  unsaturated aryl sulfone compound, wherein the mitotic phase cell cycle inhibitor is selected from the group consisting of vinca alkaloids, taxanes, naturally occurring macrolides, and colchicine and its derivatives and the topoisomerase inhibitor is selected from the group consisting of camptothecin, etoposide and mitoxantrone.

2. A method according to claim 1 wherein the cytoprotective compound has the formula I:



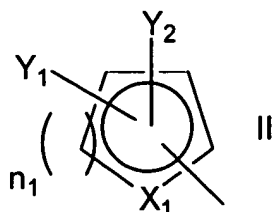
wherein:

n is one or zero;

$Q_1$  and  $Q_2$  are, same or different, are substituted or unsubstituted aryl; or a pharmaceutically acceptable salt thereof.

3. The method according to claim 2 wherein:

$Q_1$  is selected from the group consisting of substituted and unsubstituted phenyl, 1-naphthyl, 2-naphthyl, 9-anthryl and an aromatic radical of formula II:



wherein

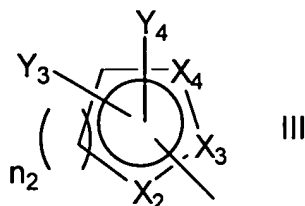
$n_1$  is 1 or 2,

$Y_1$  and  $Y_2$  are independently selected from the group consisting of hydrogen, halogen, and nitro, and

$X_1$  is selected from the group consisting of oxygen, nitrogen, sulfur and

; and 

$Q_2$  is selected from the group consisting of substituted and unsubstituted phenyl, 1-naphthyl, 2-naphthyl, 9-anthryl and an aromatic radical of formula III:



wherein

$n_2$  is 1 or 2,

$Y_3$  and  $Y_4$  are independently selected from the group consisting of hydrogen, halogen, and nitro, and

$X_2$ ,  $X_3$  and  $X_4$  are independently selected from the group consisting of carbon, oxygen, nitrogen, sulfur and

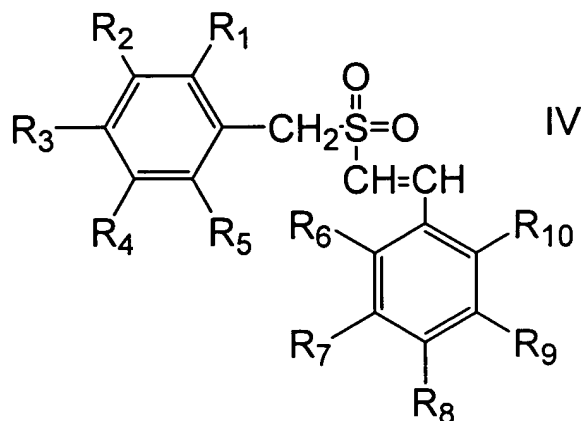


provided that not all of  $X_2$ ,  $X_3$  and  $X_4$  may be carbon; or  
a pharmaceutically acceptable salt thereof.

4. A method according to claim 3 wherein  $Q_1$  and  $Q_2$  are selected from substituted and unsubstituted phenyl.



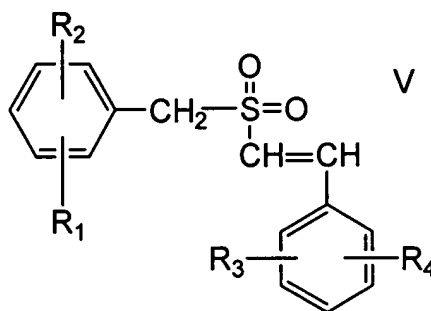
5. A method according to claim 4 wherein the cytoprotective compound has the formula IV:



wherein:

R<sub>1</sub> through R<sub>10</sub> are independently selected from the group consisting of hydrogen, halogen, C1-C8 alkyl, C1-C8 alkoxy, nitro, cyano, carboxy, hydroxy, phosphonato, amino, sulfamyl, acetoxy, dimethylamino(C2-C6 alkoxy), C1-C6 trifluoroalkoxy and trifluoromethyl; or a pharmaceutically acceptable salt thereof.

6. The method according to claim 4 wherein the cytoprotective compound has the formula V:



wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are independently selected from the group consisting of hydrogen, halogen, C1-C8 alkyl, C1-C8 alkoxy, nitro, cyano, carboxy, hydroxy and trifluoromethyl; or a pharmaceutically acceptable salt thereof.

7. The method of claim 6 wherein the cytoprotective compound is selected from the group consisting of (E)-4-fluorostyryl-4-chlorobenzylsulfone; (E)-2-chloro-4-fluorostyryl-4-chlorobenzylsulfone; (E)-4-chlorostyryl-4-chlorobenzylsulfone; (E)-4-carboxystyryl-4-chlorobenzyl sulfone; and (E)-4-fluorostyryl-2,4-dichlorobenzylsulfone.

8. (Cancelled)

9. (Cancelled)

10. (Cancelled)

11. (Cancelled)

12. The method of claim 1 wherein the cytoprotective compound is of the Z-configuration.

13. (Cancelled)

14. The method according to claim 1 wherein the cytoprotective compound is administered at least about 12 hours before administration of the mitotic phase cell cycle inhibitor or topoisomerase inhibitor.

15. The method according to claim 14 wherein the cytoprotective compound is administered at least about 24 hours before administration of the mitotic phase cell cycle inhibitor or topoisomerase inhibitor.

16. (Cancelled)

17. The method according to claim 1 wherein the mitotic phase cell cycle inhibitor is selected from the group consisting of paclitaxel and vincristine.

18. In a method for treating cancer or other proliferative disorder comprising administering an effective amount of at least one mitotic phase cell cycle inhibitor or topoisomerase inhibitor to an animal in need of such treatment, the improvement comprising administering to the animal at least about 4 hours prior to administration of the mitotic phase cell cycle inhibitor or topoisomerase inhibitor an effective amount at least one cytoprotective  $\alpha$ ,  $\beta$  unsaturated aryl sulfone compound, wherein the mitotic phase cell cycle inhibitor is selected from the group consisting of vinca alkaloids, taxanes, naturally occurring macrolides, and colchicine and its derivatives and the topoisomerase inhibitor is selected from the group consisting of camptothecin, etoposide and mitoxantrone, and wherein the animal is protected from the cytotoxic side effects of the administration of the mitotic phase cell cycle inhibitor or topoisomerase inhibitor.

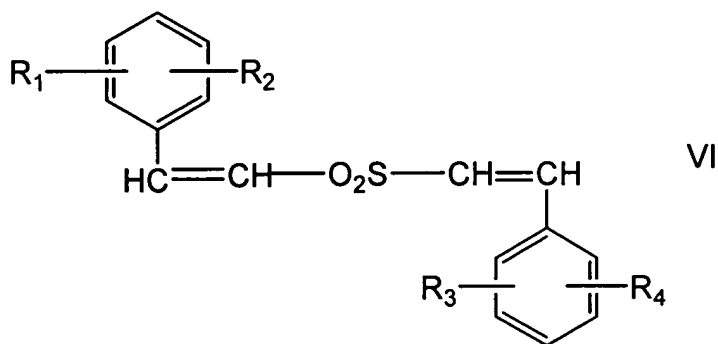
19. (Cancelled)

20. The method according to claim 18 wherein the cytoprotective compound is administered at least about 12 hours before administration of the mitotic phase cell cycle inhibitor or topoisomerase inhibitor.

21. The method according to claim 20 wherein the cytoprotective compound is administered at least about 24 hours before administration of the mitotic phase cell cycle inhibitor or topoisomerase inhibitor.

22. The method of claim 18 wherein the cytoprotective compound is selected from the group consisting of (E)-4-fluorostyryl-4-chlorobenzylsulfone; (E)-2-chloro-4-fluorostyryl-4-chlorobenzylsulfone; (E)-4-chlorostyryl-4-chlorobenzylsulfone; (E)-4-carboxystyryl-4-chlorobenzyl sulfone; and (E)-4-fluorostyryl-2,4-dichlorobenzylsulfone.

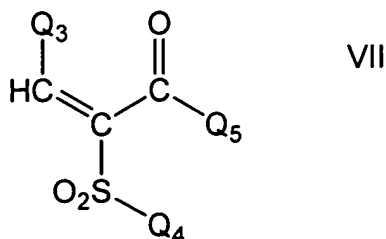
23. The method according to claim 1 wherein the cytoprotective compound is according to formula VI:



wherein:

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are independently selected from the group consisting of hydrogen, halogen, C1-C8 alkyl, C1-C8 alkoxy, nitro, cyano, carboxy, hydroxy and trifluoromethyl; or a pharmaceutically acceptable salt thereof.

24. The method according to claim 1 wherein the cytoprotective compound is according to formula VII:

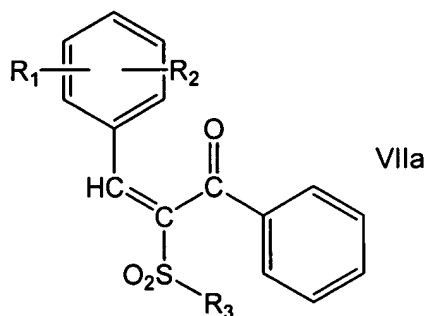


Wherein

Q<sub>3</sub>, Q<sub>4</sub> and Q<sub>5</sub> are independently selected from the group consisting of phenyl and mono-, di-, tri-, tetra- and penta-substituted phenyl where the substituents, which may be the same or different, are independently selected from the group consisting of halogen, C1-C8 alkyl, C1-C8 alkoxy, nitro, cyano, carboxy, hydroxy, phosphonato, amino, sulfamyl, acetoxy,

dimethylamino(C2-C6 alkoxy), C1-C6 trifluoroalkoxy and trifluoromethyl; or a pharmaceutically acceptable salt thereof.

25. The method according to claim 24 wherein the cytoprotective compound is according to formula VIIa:



wherein

R<sub>1</sub> and R<sub>2</sub> are independently selected from the group consisting of hydrogen, halogen, C1-C8 alkyl, C1-8 alkoxy, nitro, cyano, carboxy, hydroxy, and trifluoromethyl; and

R<sub>3</sub> is selected from the group consisting of unsubstituted phenyl, mono-substituted phenyl and di-substituted phenyl, the substituents on the phenyl ring being independently selected from the group consisting of halogen and C1-8 alkyl; or a pharmaceutically acceptable salt thereof.

26. The method of claim 25 wherein the cytoprotective compound is 2-(phenylsulfonyl)-1-phenyl-3-(4-fluorophenyl)-2-propen-1-one.

# THE MERCK INDEX

AN ENCYCLOPEDIA OF  
CHEMICALS, DRUGS, AND BIOLOGICALS

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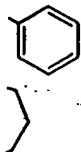
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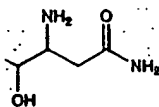
1996

ik et al., Austrian pat.  
mbH), C.A. 62, 5207e



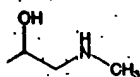
Crystalline powder, mp  
d other common organic

lmino-2,3-dideoxy-N<sup>4</sup>-(1-  
7-2-benzopyran-3-yl)-3-  
O<sub>2</sub>; mol wt 423.47. C  
45%. Major component  
iced by *Bacillus pumilus*  
mmatory activity *in vivo*.  
okai 83 18,379 (1983 to  
33); J. Itoh et al., *J. Anti-  
r. Biol. Chem.* 46, 1255  
2659. Use as acaricide:  
o Meiji Seika), C.A. 100,



er, mp 132-135° (dec). uv  
nm (ε 27300, 6400, 4380).  
iol). LD<sub>50</sub> orally in mice:

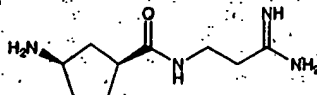
-Hydroxy-2-(methylamino)-  
; 3'-[1-hydroxy-2-(methyl-  
MJ-1996. C<sub>10</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>S;  
%, N 11.47%, O 19.65%, S  
Fr. pat. M3027 (1965) to  
la (1965); Uloth et al., *J.*  
tilates adrenergic α-recep-  
e racemate: Dungan et al.,  
(1965); Stanton et al., *ibid.*  
s, *Nature* 203, 1283 (1964);  
armacol. 10, 293 (1970);  
xicol. Appl. Pharmacol. 23,



1.1.  
N<sub>2</sub>O<sub>3</sub>S·CH<sub>3</sub>SO<sub>3</sub>H, amide-  
Fenrinol, Nalda. Crystals  
D<sub>50</sub> in female rats: 13-36  
decongestant (nasal).

lmino-N-(3-amino-3-imino-  
le; N-(2'-amidoethyl)-3-  
myxoviromycin. C<sub>25</sub>H<sub>31</sub>N<sub>7</sub>  
9.15%, N 28.26%, O 8.07%.

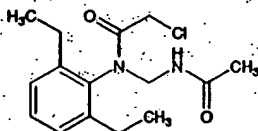
Antibiotic substance produced by *Streptomyces flavochro-  
mogenes* isolated from Japanese soil (Shioka Prefecture).  
Isoln and structure: S. Nakamura et al., *J. Antibiot.* 14A,  
103 (1961); S. Nakamura, *Chem. Pharm. Bull.* 9, 641 (1961).  
Identity with myxoviromycin: S. Nakamura et al., *J. Anti-  
biol.* 14A, 163 (1961). Prepn: Katsube, Saito, Japan, pat.  
21,418('68) (to Sumitomo), C.A. 70, 87135q (1969). Synthe-  
sis of amidinomyacin and *trans* isomer: H. Paul et al., *Arch.  
Pharm.* 301, 512 (1968). Crystal and molecular structure:  
M. Kaneda et al., *J. Antibiot.* 33, 778 (1980).



Sulfate, C<sub>25</sub>H<sub>31</sub>N<sub>7</sub>O<sub>10</sub>H<sub>2</sub>SO<sub>4</sub>, plates or needles from water +  
methanol, dec 285-288°. [α]<sub>D</sub><sup>25</sup> -3.9° (c = 3). Absorption  
spectra: S. Nakamura, *loc. cit.* Soluble in water. Practi-  
cally insol in ether, benzene, ethyl acetate, methanol, ethanol,  
butanol, acetone.

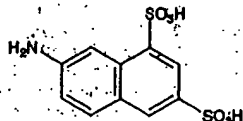
THERAP CAT: Antiviral.

420. Amidochlor. N-[(Acetylamino)methyl]-2-chloro-  
N-(2,6-diethylphenyl)acetamide; N-acetamidomethyl-2-  
chloro-2',6'-diethylacetanilide; MON-4621; Limit. C<sub>22</sub>H<sub>27</sub>  
ClN<sub>2</sub>O<sub>2</sub>; mol wt 296.80. C 60.70%, H 7.13%, Cl 11.95%, N  
9.44%, O 10.78%. Plant growth regulator for cool season  
grasses. Prepn: Neth. pat. Appl. 7,207,261; K. W. Ratts;  
U.S. pat. 3,830,841 (1972, 1974 both to Monsanto); K. W.  
Ratts, J. P. Chupp, *J. Org. Chem.* 39, 3745 (1974). Use as  
plant growth regulator: K. W. Ratts et al., U.S. pat. 3,829-  
306 (1974 to Monsanto). Effect on growth and seedhead  
suppression of annual bluegrass: A. M. Petrovic et al.,  
*Agron. J.* 77, 670 (1985); of wild and cultivated proso millet:  
J. L. Carpenter, H. J. Hopon, *HortScience* 20, 942 (1985); on  
established turfgrass: P. C. Bhowmik, *Proc. 5th Int. Turf-  
grass Res. Conf.* 735 (1985).



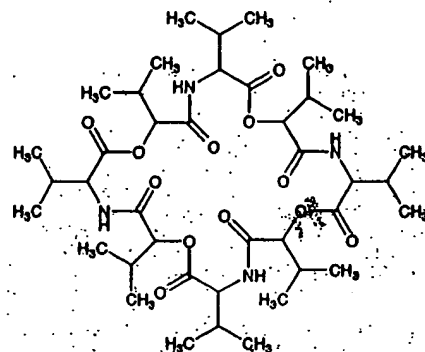
Crystals from methanol, mp 148-149°.  
USE: Turf growth regulator.

421. Amido-G-Acid. 7-Amino-1,3-naphthalenedisul-  
fonic acid; 2-naphthylamine-6,8-disulfonic acid; amino-G-  
acid. C<sub>10</sub>H<sub>7</sub>NO<sub>4</sub>S<sub>2</sub>; mol wt 303.32. C 39.60%, H 2.99%, N  
4.62%, O 31.65%, S 21.14%. Prepd by sulfonation of β-  
naphthylamine: Pierz-David, Braunschweig, *Helv. Chim.  
Acta* 6, 1146 (1923).



Tetrahydrate, fine monoclinic needles. Sol in water, less  
sol in alc. Soly in water at 20°: 9.24 g in 100 g of satd soln.  
USE: Manufacture of dyes.

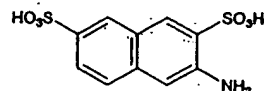
422. Amidomycin. C<sub>40</sub>H<sub>59</sub>N<sub>9</sub>O<sub>13</sub>; mol wt 797.00. C  
60.28%, H 8.60%, N 7.03%, O 24.09%. Antibiotic substance  
produced by an unidentified *Streptomyces* culture (PRL  
1642). Composed of 4 moles each of D-(-)-valine and D-  
(-)-α-hydroxyisovaleric acid, linked alternately by ester  
and amide bonds to form a 24-membered ring: Vinling,  
Taber, *Can. J. Chem.* 35, 1109 (1957). Structure studies:  
Shemyakin et al., *Tetrahedron Letters* 1963, 351, *Tetrahe-  
dron* 19, 995 (1963).



D-amino acids only

Needles from dilute ethanol or petr ether, mp 192°. [α]<sub>D</sub><sup>25</sup>  
+19.2° (c = 1.2 in ethanol). Neutral reaction. Practically  
insol in water. Readily sol in most organic solvents. Pri-  
marily active against yeasts.

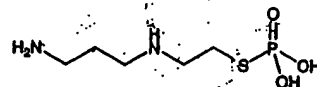
423. Amido-R-Acid. 3-Amino-2,7-naphthalenedisul-  
fonic acid; 2-naphthylamine-3,6-disulfonic acid. C<sub>10</sub>H<sub>7</sub>  
NO<sub>4</sub>S<sub>2</sub>; mol wt 303.32. C 39.60%, H 2.99%, N 4.62%, O  
31.65%, S 21.14%. Prepd by treating 2-hydroxy-3,6-naph-  
thalenedisulfonic acid with ammonium sulfite and ammo-  
nium hydroxide: Petitcolas, Josué, *Bull. Soc. Chim. France*  
1952, 89.



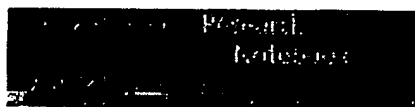
Crystals or powder. Soluble in water. Solutions show a  
violet-blue fluorescence.

USE: Manufacture of dyes.

424. Amifostine. 2-[(3-Aminopropyl)amino]ethane-  
thiol dihydrogen phosphate ester; phosphorothioic acid S-[2-  
[(3-aminopropyl)amino]ethyl] ester; aminopropylaminoethyl  
thiophosphate; ethiofos; gammaphos; SAPEP; NSC-296961;  
WR-2721; YM-08310; Ethiol. C<sub>7</sub>H<sub>15</sub>N<sub>3</sub>O<sub>3</sub>PS; mol wt  
214.23. C 28.03%, H 7.06%, N 13.08%, O 22.41%, P  
14.46%, S 14.97%. Thiophosphate derivative of cysteamine,  
q.v.; provides normal cells with selective protection against  
the toxic effects of cancer chemotherapy and radiation treat-  
ment. Prepn of monohydrate: J. R. Piper et al., *J. Med.  
Chem.* 12, 236 (1969); J. R. Piper, T. P. Johnston, U.S. pat.  
3,892,824 (1975 to Southern Res. Inst.). Differential radio-  
protective activity: J. M. Yuhias, J. B. Storer, *J. Nat. Cancer  
Inst.* 42, 331 (1969). Mechanism of action study: G. D.  
Simoluk et al., *Cancer Res* 48, 3641 (1988). Bioavailability:  
L. Fleckenstein et al., *Pharmacol. Ther.* 39, 203 (1988).  
Clinical pharmacokinetics: L. M. Shaw et al., *ibid.* 195,  
HPLC determin in plasma: N. F. Swynnerton et al., *Int. J.  
Radiat. Oncol. Biol. Phys.* 12, 1495 (1986). Review of devel-  
opment as radioprotector: D. Q. Brown et al., *Pharmacol.  
Ther.* 39, 157-168 (1988); of role in chemotherapy: R. L.  
Capizzi et al., *Cancer* 72, 3495-3501 (1993); M. Tréakes, W.  
J. M. van der Vijgh, *Cancer Chemother. Pharmacol.* 33, 93-  
106 (1993).



Monohydrate, white solid from methanol/ether, mp 160-  
161° (dec). LD<sub>50</sub> in mice (mg/kg): 700 i.p. (Piper, John-  
ston).



## Cytoprotectant Amifostine Approved

The FDA has approved a new cytoprotective agent -- amifostine (Ethyol/US Bioscience) -- for reducing the cumulative renal toxicity associated with repeated cisplatin therapy in patients with advanced ovarian cancer. Amifostine is an organic thiophosphate prodrug that is rapidly dephosphorylated in tissues to a pharmacologically-active free thiol. This thiol compound binds and detoxifies reactive cisplatin metabolites, and also scavenges free radicals generated in tissues exposed to cisplatin. Since amifostine reaches a higher concentration in normal tissue relative to tumor tissue, it is able to reduce cisplatin's renal toxicity without compromising the antitumor efficacy. First developed to protect tissues against radiation damage, amifostine has since proved to be effective for protecting against hematologic toxicity in patients receiving cisplatin, cyclophosphamide, and/or mitomycin, and to reduce cisplatin-induced nephrotoxicity, ototoxicity, and neurotoxicity. In clinical trials, patients treated with amifostine showed a reduction in neutropenia-related fever and sepsis and spent fewer days in the hospital and/or on antibacterial therapy, compared with patients who did not receive amifostine. Moreover, fewer patients discontinued therapy before completing the scheduled number of treatment cycles. Amifostine is given intravenously as a 15-minute infusion of 910 mg/m<sup>2</sup> starting 30 minutes prior to cisplatin therapy.

The drug is rapidly cleared from plasma; distribution half-life is less than one minute and elimination half-life is about 8 minutes. Less than 10% of amifostine remains in the plasma 6 minutes after administration. The most common side effects are transient reduction in blood pressure, nausea, vomiting, somnolence, and sneezing. Less common side effects include flushing, hypocalcemia, and hiccups. Antiemetics reduce the nausea (pretreatment with dexamethasone or metoclopramide has no effect on pharmacokinetics). Contraindications include hypotension, dehydration, hypocalcemia, or sensitivity to aminothiols compounds or mannitol (the vehicle). US Bioscience is continuing Phase II and III trials to evaluate the effects of ethyol for protecting against radiation damage in patients treated for tumors of the rectum, cervix, lung and neck. It is also under investigation for its ability to sensitize a tumor to therapy. It is in trial for use with Bristol-Myer's taxol, allowing escalation of the dose to more than twice the dosage currently used in clinical practice. US Bioscience developed amifostine and owns the patents; Alza has exclusive marketing rights in the US for five years; Schering-Plough is marketing the drug in Europe; and Lilly is planning to introduce it in Canada. (Spencer CM, Goa KL. Drugs 1995;50:1001-1031. Additional information from Alza.)

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 AN 1998287056 EMBASE  
 TI Reducing the toxicity of anticancer therapy: New strategies.  
 AU Griggs J.J.  
 CS J.J. Griggs, University Rochester Cancer Center, 601 Elmood Avenue,  
 Rochester, NY 14642, United States  
 SO Leukemia Research, (1998) 22/SUPPL. 1 (S27-S33).  
 Refs: 34  
 ISSN: 0145-2126 CODEN: LEREDD  
 PUI S 0145-2126(98)00036-8  
 CY United Kingdom  
 DT Journal; Conference Article  
 FS 016 Cancer  
 025 Hematology  
 030 Pharmacology  
 037 Drug Literature Index  
 038 Adverse Reactions Titles  
 052 Toxicology  
 LA English  
 SL English

=> d ab

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 AB Cytoprotective agents offer opportunities to reduce the treatment-related toxicity of anticancer therapy and perhaps to increase the dose and dose intensity of radiation and chemotherapy. One such agent is amifostine, an organic thiophosphate. Amifostine selectively protects normal tissues and provides broad-spectrum protection for a variety of organs while remaining minimally toxic. Clinical studies have demonstrated that amifostine protects against myelotoxicity, nephrotoxicity, neurotoxicity, mucositis and esophagitis in patients treated with alkylating and platinum agents, paclitaxel and radiation therapy. In addition, preclinical studies suggest the possibility of protection against anthracycline induced cardiotoxicity and radiation- and chemotherapy-induced mutagenicity. Preclinical and clinical studies have not demonstrated any diminution of antitumor efficacy. Amifostine is well tolerated in doses of 740 or 910 mg/m<sup>2</sup>. The most common side effects requiring treatment are transient hypotension, which responds to intravenous fluids, and nausea and vomiting, effectively treated with 5-HT<sub>3</sub> antagonists and dexamethasone.